DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

VACCINES AND RELATED BIOLOGICAL PRODUCTS

ADVISORY COMMITTEE BY TELECONFERENCE

Thursday, October 16, 1997

12:30 p.m.

National Institutes of Health
Building 29N
Room 121
Bethesda, Maryland

PARTICIPANTS

Patricia L. Ferrieri, M.D., Chairperson
Nancy Cherry, Executive Secretary

MEMBERS

Adaora A. Adimora, M.D.
Mary Lou Clements-Mann, M.D.
Rebecca E. Cole (Consumer Member)
Mary K. Estes, Ph.D.
Harry B. Greenberg, M.D.
Alice S. Huang, Ph.D.
Gregory A. Poland, M.D.
Fernando V. Villalta, Ph.D.

CONSULTANT

Claire V. Broome, M.D.

FDA

Dr. Neil Goldman
Dr. Bascom Anthony
Dr. Drusilla Burns

C O N T E N T S

P R O C E E D I N G S

Call to Order

DR. FERRIERI: This is Dr. Pat Ferrieri, Chair of the Vaccines and Related Biological Products Advisory Committee.

I want to thank all of the committee members who are able to be with us for their participation. I hope you will stay for the entirety. We will try to make this as concise and targeted as possible, so that we will adjourn before the stated time, but please don't leave. We need you for your participation.

I would like to now turn it back to Ms. Cherry from FDA for any announcements.

Announcements

MS. CHERRY: Let me first add my welcome and thank you to all of you also. The purpose of today's teleconference is to complete the review of the Laboratory of Pertussis, which started with the site visit on September 5th. Today, as a committee, you will taking action on the report of the site visit team, which by the way was chaired

by Dr. Ferrieri.

Because this is a teleconference you must announce your name each time before you speak. If you are cut off, the number to call to be reinstated is 1-700-288-2000. When you dial that, you ask for conference number 708805. It is

on the sheet of paper that you received yesterday from us, too. Use the mute button on your phone if you have one, but please do not use the hold button. If you can close your office door or do anything else to damp any background noise, that would be very helpful.

We will have a short open session and then we will close the meeting for committee deliberations.

Before I read the COI statement, there is one other announcement. Dr. Poland, are you there?

DR. POLAND: Yes, I am.

MS. CHERRY: Dr. Poland would like a minute to make a statement.

DR. FERRIERI: Go ahead, Greg.

DR. POLAND: The main thing that I wanted to say was I was upset recently to learn courtesy of Peter Patriarca that significant misinterpretation and misquote of some work I presented at a scientific meeting recently was reported in Vaccine Weekly. I thought it was worthwhile to make this group aware of that. It had to do with the recall of the influenza vaccine.

If there are any questions that anybody has, I am happy to address, otherwise, I just was going to say that the accurate and proper report of those comments have been published September 24th in the Journal of the American Medical Association. So if questions come up or people say,

well, how could this individual say something like that, I just want people to know that the report in Vaccine Weekly is inaccurate and the proper report is in JAMA.

DR. FERRIERI: Thank you, Greg. We totally understand. We don't believe anything we read --

DR. POLAND: It is quite frustrating to have something that important --

DR. FERRIERI: I understand. We share your agony and appreciate your trying to clarify that with us.

Is there any other announcement?

MS. CHERRY: Well, I do need to read the Conflict of Interest Statement.

DR. FERRIERI: Yes, please, Nancy.

MS. CHERRY: This announcement is made a part of the record at this meeting of the Vaccines and Related Biological Products Advisory Committee on October 16, 1997. Pursuant to the authority granted under the Committee Charter, the Director of the Center for Biologics Evaluation and Research has appointed Dr. Claire Broome as a temporary voting member.

Based on the agenda made available, it has been determined that all committee discussions at this meeting for a review of the intramural research program for the Laboratory of Pertussis, Division of Bacterial Products, present no potential for a conflict of interest.

In the event that the discussions involve specific products or firms not on the agenda for which FDA participants have a financial interest, the participants are aware of the need to exclude themselves from such involvement, and their exclusion will be noted for the public record.

With respect to all other meeting participants, we ask in the interest of fairness that they address any current or previous financial involvement with any firm whose products they wish to comment on.

DR. BROOME: Nancy, this is Claire Broome. I have been here all along, but the phone mike didn't seem to be working.

MS. CHERRY: I am glad to have you here.

That is the end of my Conflict of Interest Statement, so it is now back to Dr. Ferrieri.

DR. FERRIERI: Thank you, Nancy.

We will start then with the introduction to the program by Dr. Neil Goldman, Associate Director for Research at CBER.

Good afternoon, Dr. Goldman.

DR. GOLDMAN: Good afternoon. I will give you something briefly.

DR. FERRIERI: Thank you.

Introduction

DR. GOLDMAN: I would like to thank all of you for participating in this teleconference to review the results of the site visit for the Laboratory of Pertussis. As you aware, I am sure as part of your responsibilities as the advisory committee, which includes such things as technical advice on biological products, classes or groups of products, advice on the appropriate design of clinical trials, advice on the use of surrogate markers for clinical endpoints, advice on interpretation of the results of clinical protocols, and general advice on risk assessment, another responsibility is the peer review of our intramural research programs and the research scientists who participate in them.

As you know, while academicians usually are reviewed each time they submit and obtain a grant, our laboratories which are funded intramurally are reviewed every four years by a subgroup of you, the advisory committee. This mechanism is very similar to that which the NIH uses for their periodic review of their laboratories.

Now, historically, research has been an integral

part of the mission of CBER, which is to protect and enhance the public health through regulation of biological and related products including blood, vaccines, and biological therapeutics according to statutory authority.

Now, the regulation of these products is founded

on science, as well as law, to ensure their purity, potency, safety, efficacy, and availability. Now, to fulfill this mission, we therefore conduct research as an essential element of science-based decisionmaking on regulatory issues.

Uniquely, among the other centers of FDA, we were mandated in 1955 by a PHS order that we shall conduct research on problems related to vaccines, serums, antitoxins, and analogous products including blood and its derivatives, and we shall conduct other studies to assure safety, purity, and potency of biological products, to improve existing products, and to develop new products.

The research that goes on in this particular laboratory certainly highlights these last two objectives, and you will probably have read about the research in pertactin, the work on secretory mechanisms, as well as the standards and methods that were developed for both potency and immunogenicity of the pertussis vaccine.

Now, you are also I think well aware that in CBER we have been operating under the researcher reviewer model

in which all researchers are fully integrated into the review process. The regulatory duties therefore include review of INDs, PLAs, and BLAs, development and presentation of regulatory policy, meetings with manufacturers, sponsors, and meetings with you, the advisory committee.

Researcher reviewers also perform annual and prelicense inspections, and the percentage of time which these researcher reviewers spend on regulatory responsibilities is usually commensurate with the length of time they have been with us and can vary anywhere from 10 to 50 percent.

The types of research which we consider mission related include research on specific products that are under an active IND or license application, research on a specific policy issue related to a product or product class, disease area, or therapeutic modality to provide the foundation for evaluating future INDs and license applications that will be submitted, and research associated with the development of methods and standards to which products can be compared.

Now, the request to you, VRBPAC, as was originally related to the site visit team which Dr. Ferrieri chaired, is to assess -- and that is considering both strengths and weaknesses -- the quality and appropriateness to the regulatory mission of the research being conducted, which includes the relevance, originality, creativity, and level

of sophistication, and also to evaluate the accomplishments of the individual scientist, which include demonstration of independence, productivity, the validity of their approaches, and research stature.

In addition, we have asked the site visit team and

thus through them, this full committee as well, to provide advice on the current scientific direction of the research program, whether new directions should be considered, any changes in the way a research program is administered, or the level and utilization of the resources.

Lastly, and very importantly, we asked for any advice on promotion or conversion, for example, to senior investigator or staff scientist, of some of our designated personnel. In particular, we are asking the appropriateness at this time.

Ultimately, the final report of the site visit team which is approved by this full advisory committee will be sent to the Center Director, Dr. Zoon, who will then pass it on to the appropriate office and division director. That will be Dr. Hardegree and Dr. Anthony, who is with us today, and finally down to the lab chief, Dr. Burns, who is with us today, and even to the investigator who was reviewed.

Any responses to comments in the final report will be prepared, and these responses will be forwarded back to your committee.

Thus, the final report, which peer reviews our research programs and the scientists who participate in them, is a critical tool for us to effectively manage the research programs in the center, as well as aiding us in making important personnel decisions.

The need for a comprehensive, in-depth evaluation is especially true in these times of reduced resources when stringent research priorities must be set.

I now would like to turn this back to Dr. Ferrieri and I would like to thank Dr. Ferrieri for the opportunity to speak to the committee today.

DR. FERRIERI: Thank you very much, Dr. Goldman.

We will move on then with the agenda. Next will be Dr. Bascom Anthony, who is the Director of Division of Bacterial Products, who will give us a brief overview.

Good afternoon.

Overview of the Division of Bacterial Products

DR. ANTHONY: Good afternoon, Pat, and other committee members. I will be brief. I don't think you really need an overview of the division.

We have five laboratories and the Pertussis Laboratory is one of those. I just have three brief comments to make about the Pertussis Lab concerning events there since the last review.

The first, of course, is that there is a new lab

chief, Dr. Burns, who has been in charge I think for probably three of the five years since the last review.

The second remark is that there has been some shrinkage in the size of this group due to a variety of causes, some organizational, most of them were personal

reasons, and one was the tragedy in the death of Dr. Roberta Shahin.

The consequence of all this is that they now operate with a group of approximately 12, only 10 of whom are on government FTEs, whereas, at the last review there were 17 scientists in that laboratory.

The shrinking resources in personnel is complicated by our inability at the present time, and for some time past, to replace individuals as they leave, and this is part of the shrinking resources situation that Dr. Goldman mentioned, and we can only hope that this will not go on indefinitely in this same direction.

In the face of these changes, this group has had an enormous regulatory load primarily as a result of the development and clinical trials of the new acellular pertussis vaccines.

Since the last review and before the completion of the last rounds of those trials, this group took the lead in licensing two new combination vaccine products. They were heavily involved throughout the Phase I, Phase II, and Phase

III studies both in planning and in actively collaborating with the investigators, and since the completion of those studies, most of which wound up in the spring and summer of 1995, they have been presented with six new product license applications, three of which they have turned around and

approved, and the others they are working on very busily.

They have had to treat these as priority applications, that is, instead of the standard review time of one year under the User Fee Act of 1992, the acellular vaccine applications were designated as priority applications by Dr. Zoon, and our pertussis laboratory group and their colleagues in other parts of the center have responded by turning these applications around in a period of about six months.

So with those remarks in mind, I hope you may have a framework in which to evaluate the research accomplishments of this group.

Thank you again for all of your support and your hard work in the review.

DR. FERRIERI: Thank you very much, Dr. Anthony.

We will move ahead then.

DR. HUANG: May I ask a question, please?

DR. FERRIERI: Please identify yourself.

DR. HUANG: Yes? May I ask a question, please?

DR. FERRIERI: Yes, you may. Please identify

yourself.

DR. HUANG: This is Dr. Alice Huang. I am asking Dr. Anthony if there were further or are there any more vaccine applications in 1997.

DR. ANTHONY: Yes. We have 300 active review that

are in various stages. I think all of those were submitted before the end of '96 -- no, no, that is not correct. Help me, Dr. Burns.

DR. BURNS: Yes, they were all submitted before 1997. These are the acellular pertussis vaccines you are talking about?

DR. HUANG: Right.

DR. BURNS: Yes.

DR. ANTHONY: We have some other combination products that include acellular pertussis vaccines that are also under review, but new acellular vaccines, six applications, three have been approved.

DR. HUANG: But there have been no new applications submitted since January of 1997?

DR. ANTHONY: Not for new acellular pertussis vaccines, correct.

DR. HUANG: Thank you.

DR. FERRIERI: We will move ahead then.

Dr. Drusilla Burns, who is Chief of the Laboratory of Pertussis, will give us a very brief overview on the

goals and research activities.

Drusilla.

Research Activities and Goals in the

Laboratory of Pertussis

DR. BURNS: First, I would like to thank everybody

for taking time out from your schedules for this phone call, and I will be brief, but I would like to take a few minutes of your time to give you some background information about the Laboratory of Pertussis.

The laboratory really has two primary responsibilities. We are responsible for the regulation of pertussis-containing vaccines and, secondly, we conduct research on Bordetella pertussis and the host response to this organism.

The laboratory is structured into three sections, each of which represents a specific area of expertise that is needed to regulate the pertussis vaccines. The three sections are: the Molecular Microbiology Section, providing expertise in the areas of microbiology and genetics; the Biochemistry Section, providing expertise in the areas of biochemistry and molecular biology; and the Applied Immunology and Vaccine Evaluation Section, providing expertise in more applied areas, such as clinical assay development and control testing, so the structure of the laboratory is really based upon our regulatory needs and

responsibilities.

Our research programs range from basic research designed to understand better the pathogenic mechanisms of Bordetella pertussis to the more applied research needed for the development of assays that are used to measure clinical

responses to pertussis vaccines and to assess the safety and potency of these vaccines.

Current research projects include studies on proteins, such as pertussis toxin, FHA, and pertactin, which as you are aware, are proteins that have been shown to be protective antigens in both animal models and in humans, and we are studying these proteins in the hope of better understanding the role that they play in disease and host protective mechanisms.

We are also studying proteins produced by Bordetella pertussis that are not found in any of the current vaccines and that may be useful in the diagnosis of disease or which may tell us more about the disease process.

In addition, we are examining alternate delivery systems for vaccine antigens. Our Applied Immunology and Vaccine Evaluation Section conducts laboratory research studies that are aimed at improving diagnostic methods and serological assays that are so essential for the clinical evaluation of pertussis vaccines.

In addition, this section of the laboratory has

standardized the toxicity tests and potency tests for acellular pertussis vaccines that are used to ensure the safety and potency of every lot of pertussis vaccine manufactured by U.S. licensed manufacturers.

The goals of our research program are twofold.

First, we hope to generate information that will be used: one, to improve pertussis vaccines; two, to improve our ability to evaluate these vaccines both in the laboratory and in the clinic; and, three, to improve our understanding of the mechanism by which these vaccines protect.

Secondly, and very importantly, our research gives us the hands-on experience that is so essential for proper evaluation of the technologies that are used in the manufacture and testing of current vaccines, and those technologies that are being considered for the manufacture and testing of future pertussis vaccines.

As I indicated, we both conduct research and regulate pertussis-containing vaccines. Since we spend a considerable amount of time on our regulatory responsibilities, I would like to briefly describe them to you. You heard a little bit about this from Dr. Anthony, but maybe I can go into it in just a bit more detail.

Since you are members of the advisory committee, you are very well aware that our regulatory load was particularly heavy in the last few years due to the desire

on everyone's part to get the acellular pertussis vaccines tested and licensed as quickly as possible.

Since 1992, the members of the Laboratory of Pertussis have reviewed over 950 IND submissions. Approximately 50 of these submissions were original

submissions that contained considerable amounts of manufacturing and preclinical information.

The staff of the Laboratory of Pertussis served as reviewers and chairpersons for a number of product license applications, and Dr. Anthony went through those just a minute ago.

The Applied Immunology and Vaccine Evaluation Section of the laboratory also conducts the routine control testing of both acellular and whole-cell pertussis vaccines. In the past five years, this section has performed approximately 750 potency tests and 450 toxicity tests.

This section also spends a considerable amount of their time assisting manufacturers prior to the vaccine licensing in the development of their own in-house potency and toxicity tests.

Now, the regulatory load carried by the Laboratory of Pertussis in the last five years would be considered to be heavy by anyone's standards, and I think that is a fair statement. Everybody in the laboratory has really worked very hard to get the acellular pertussis vaccines out to the

public as quickly as possible including some of the more junior investigators in the laboratory who really put their own research careers on hold while they worked to get these vaccines licensed.

While the research in the lab may have slowed

during this period, I know it is fair to say that everybody in the laboratories absolutely would be thrilled to have been part of getting these vaccines out to the public as quickly as possible.

Now that the acellular vaccines have been licensed, the question naturally arises as to what the laboratory will be doing in the future.

As far as our regulatory responsibilities are concerned, I can assure you that we will be very busy in the next five years with the evaluation of the additional acellular pertussis vaccines, as well as the evaluation of a number of combination vaccines that contain pertussis components.

Because of the improved safety profile of acellular pertussis vaccines, as you know, interest has been generated in pertussis vaccines for adults and adolescents and of course, the members of this laboratory will be reviewing the data concerning these vaccines.

Eventually, we expect to see even further improvements in pertussis vaccinology including novel

delivery systems or perhaps the use of novel adjuvants that are capable of modulating the immune response of the recipient in very defined ways.

As always in science, things are constantly changing and evolving, and we have to be prepared for these

changes and for the products that will be coming in the future. We feel that our current research programs and directions are designed with this purpose in mind and that they will provide us with the information that we need to properly control current pertussis vaccines and will prepare us for the products that will be seen in the future.

Thank you.

DR. FERRIERI: Thank you very much, Drusilla.

It has been our habit at this point in these types of teleconferences to now clear the room.

[The committee went into closed session at 12:55 p.m.]

[2:06 p.m.]

Open Public Hearing

DR. FERRIERI: Nancy, with your permission, and the committee's permission, I am afraid we have to move now to this entity known as the Open Public Hearing. The room can be opened.

MS. CHERRY: Denise just did check the hall and there is no one there who wishes to make a statement, there is no one who wishes to rush into the room.

DR. FERRIERI: No one from the press is waiting with bated breath?

MS. CHERRY: I don't believe so. I think she would have noticed some TV cameras waiting out there.

DR. FERRIERI: Is there anything else you would like us to know, Nancy, at this point? Everyone should know about the upcoming meeting.

MS. CHERRY: Yes. The meeting is planned now for December 11th and 12th, and it looks like it will be a full two days, so full, in fact, that we have the joy of another one of there teleconferences to schedule in December. I

think we were looking at the 3rd.

Is there anyone who can tell me right now that they would not be available for one of these teleconferences on the 3rd to do a lab review, the 3rd of December?

DR. POLAND: This is Greg Poland. That date works

for me.

DR. FERRIERI: December 3rd.

MS. CHERRY: It actually is just a few days before you come into town for the December 11th and 12th meeting, but rather than keep you for an extra day, we thought we would do it by teleconference.

DR. FERRIERI: While we have your undying attention here, as best you can, unless you have clinical obligations that bring you back to your home site, or some other very urgent issue, try not to leave in the middle of the afternoon on the second day. This creates a problem when we are dealing with issues that we might have to vote on. I do appreciate how everyone wants to be able to leave, but try to make your plane reservations that give you the ability to last through the agenda that comes to us.

If there isn't anything else, then, I would move for adjournment. I want to thank all of you for staying with us to the end, your valuable contributions, and I look forward to seeing you all in December.

There will be other teleconferences and I am

leading a team November 17th for the Polysaccharide Lab at CBER. This is sort of the lay of the land and the way others have done it, and I think we have done very well for an hour and half to have covered this ground as well as some of these critical issues, fundamental and philosophical

issues.

MS. CHERRY: I would like to express my appreciation to everyone for their help to FDA.

DR. GOLDMAN: Yes, I would like to second that. We cannot do this without you, and we appreciate all of your support, in fact, and wish to provide you with all the information we can, so that in many cases, you can really get a true picture of not just the research we do -- which I also think is high quality and relevant -- but also the conditions we are going to have to do this under.

DR. FERRIERI: I think with that we can say good-bye and we will see you soon.

[The proceedings were adjourned at 2:10 p.m.]

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